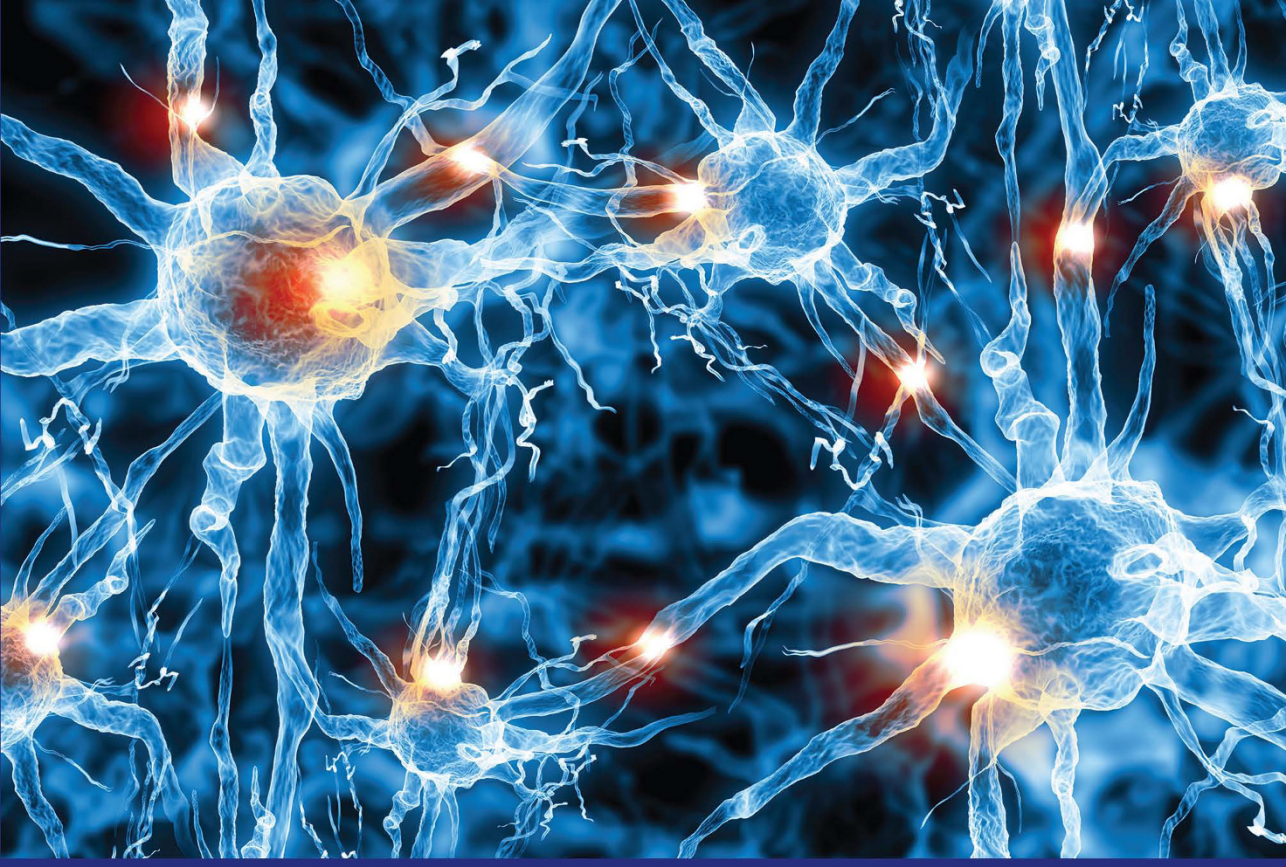

CHARLES CLARKE

NEUROLOGY

A CLINICAL HANDBOOK

WILEY

Neurology: A Clinical Handbook

Neurology: A Clinical Handbook

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This Handbook is based on the Second Edition of *Neurology: A Queen Square Textbook*, which was co-edited by Dr Clarke.

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Preface

In my training in the 1970s I was guided by many clinicians and also by books. Those large neurology tomes were useful, but it was the smaller texts that gave me insight into clinical practice. One by Dr Bryan Matthews, later Professor of Clinical Neurology at Oxford, was *Practical Neurology* published in 1963, when Matthews was a general neurologist in Derby. His was a book I could enjoy. Some comments are etched in my memory:

'There are many admirable textbooks of neurology but it is a matter of common observation that they are of more assistance in the passing of written examinations than in the management of practical problems'. Another, quoting Sir Geoffrey Jefferson, remarked ' . . . in life the tracts are not marked in red . . .'

And, from Matthews on dizziness: ' . . . there can be few physicians so dedicated to their art that they do not experience a slight decline in spirits on learning that their patient complains of giddiness.. . .'

There was thus some logic in taking *Neurology: A Queen Square Textbook*, Second Edition, the major reference work that I initiated and edited with colleagues, and turning it into this shorter, practical book. I hope this *Handbook* will serve two purposes. First, it is to be *read* – each chapter aims to give a brief overview of an area of neurology. Secondly, this book, a synopsis of our subject, provides a pointer to *Neurology: A Queen Square Textbook* in its forthcoming Third Edition, a completely separate project that has been fully updated and enhanced by Robin Howard, Dimitri M. Kullman, David Werring, and Michael Zandi. *Neurology: A Clinical Handbook* is based on the second edition of *Neurology: A Queen Square Textbook*. The editors and authors of *Neurology: A Queen Square Textbook* have not been involved in the development of this Handbook.

I struggled with several things. First: references. I decided, because one can source most references rapidly on a mobile phone, I would focus only on those references of personal interest. These are largely my own – but with one paper from my late wife Dr Ruth Seifert on *khat* and another from my father Professor Sir Cyril Astley Clarke on fatal methyl bromide poisoning – from the 1940s; both are in Chapter 19. Well, I thought . . . this is *my* book.

Secondly, with radiology: the internet is full of excellent neuroradiology (e.g. Radiopaedia *et al.*) that far surpasses printed images. Do please search for such sources – some are mentioned via the additional notes and references on my website:

https://www.drcharlesclarke.com.

My main experience for some 40 years, like that of Bryan Matthews, has been as a general neurologist in UK district general hospitals, largely the busy battleground of Whipps Cross, but always attached to a major neurology unit, initially St Bartholomew's and latterly Queen Square. I always found the variety within general neurology more attractive than its emerging specialties. I also broadened my experience by working further afield – during a meningococcal epidemic in Boston, in a leprosy clinic in Mysore, south India and elsewhere in India, Nepal and China, often in remote situations on mountaineering expeditions.

I thank many people. My parents Cyril and Féo Clarke were distinguished medical researchers, but I suspect they often despaired of me – their practical son who seemed focused on clinical practice and mountaineering, rather than research and publications. But they always gave me encouragement. Robin Coombs and Peter Lachmann grounded me in immunology at Cambridge. John Newsom-Davis and Angela Vincent took me into the world of myasthenia at the Royal Free, and my colleagues at Queen Square made *Neurology: A Queen Square Textbook* both a reality and the source of this book. They are acknowledged personally in each chapter. Wiley commisioned this book and Simon Shorvon suggested I write it.

Within the chapters, Dame Sally Davies and Dr Elizabeth Davies helped me with aspects of public health. Professor Peter Garrard guided me through cognition and dementia. Michael Hayle helped me with the nomenclature of recreational drugs. Professor Kailash Bhatia and Dr Eion Mulroy provided an excellent video of movement disorders (Chapter 7), hosted securely in my website. The new neuroanatomy illustrations were generously provided by Professor Thomas Champney, a fellow yachtsman, I soon discovered, of Miller School of Medicine, University of Miami, Florida – from his excellent book *Essential Clinical Neuroanatomy*, Wiley Blackwell 2016.

I also searched outside Queen Square, from our former alumni. I found willing and valued contributors, especially to neuroradiology – Professor Raymond Cheung in Hong Kong and Dr Patricio Paredes and Dr Pablo Soffia in Chile.

Why Chile? My partner, Professor Dame Marcela Contreras qualified in Santiago before emigrating to England, long long ago – and she has provided me with immeasurable support.

My daughters Rebecca and Naomi, who have carried their grandfather's 'Astley' into their successful business careers, have also helped, if distantly, by asking repeatedly *'Dad, when are you going finish this book?'*

My publishers Wiley have taken the project to its conclusion, smoothly and helpfully - in particular Mandy Collison, Managing Editor and Sophie Bradwell, Associate Editor for Clinical Medicine in the UK, Hari Sridharan and Sathishwaran P, Content Refinement Specialists in Chennai, South India.

Lastly, and to acknowledge the value of her expertise, Sallie Oxenham in Paris has worked tirelessly on my website design and its content. Also, two MacBook Air computers have been my constant companions – and I have retained not a page of paper. Both computers were stolen several years ago, but Dropbox provided backup without a word being lost – unlike T.E. Lawrence, who mislaid the manuscript of *The Seven Pillars of Wisdom* on Reading Station in 1919 and had to rewrite the entire book from memory.

In my study I have a portrait of Dr Thomas Sydenham, my distant grandparent, with a note from my 19th and 20th century Leicester grandfather Dr Astley Vavasour Clarke, whom also I never knew – a picture that Astley V. had left to my father. If genes have a role in these endeavours, they probably had a hand in this too.

Charles Astley Clarke
March 2022
https://www.drcharlesclarke.com

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The National Brain Appeal

A proportion of the royalties from *Neurology: A Clinical Handbook* are donated to The National Brain Appeal. The charity raises funds to advance treatment and research at the National Hospital for Neurology & Neurosurgery and the UCL Institute of Neurology – *Queen Square*. Donations are used to improve outcome and quality of life for the one in six people affected by a neurological condition, by supporting pioneering research and helping to train tomorrow's clinicians.

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Foreword

As a medical specialty, neurology emerged in its modern guise in the second half of the nineteenth century, and it was then that the National Hospital at Queen Square opened its doors, the very first hospital in the world dedicated to neurological diseases. Since then, the stories of neurology and of the hospital have been intertwined. Throughout the twentieth and now the twenty-first centuries, *Queen Square* as it has become known has maintained its position at the cutting edge of neurology and remains one of the leading neurological institutions globally, both in terms of superlative clinical care and research. As neurology developed, the *Queen Square* clinical method evolved, a method that remains the standard approach to the diagnosis and treatment of neurological conditions.

Embedded in a knowledge of the anatomy, physiology and mechanisms of disease, this clinical method has at its core the taking of a detailed history, the performance of a systematised clinical examination, the judicious choice of well-focused investigation and a balanced approach to evidence-based treatment. The diagnostic approach is successful because it is a logical exploration of symptoms aligned to the principles of nervous system structure and function. Investigations, notably neuroimaging, neurophysiology and molecular biology, have also evolved enormously and assist this process. In terms of treatment, the parallel developments of surgical and medical therapies, also rooted in the modern neurosciences, have changed neurology from being what was essentially a diagnostic specialty to a therapeutic one. Again, *Queen Square* has been at the forefront. Linked to the science has been an emphasis on ensuring that the medical process is patient centred and responsive to patient needs. In view of these spectacular advances, neurology today would be hardly recognisable to its practitioners of long ago, yet this approach throughout the world remains the cornerstone for diagnosis and treatment. It also forms the backdrop to this book.

With advancing knowledge has come increasing subspecialisation. This has undoubtedly advanced the science of neurology but has had the drawback of narrowing of scope of individual medical practice. One solution is to incorporate the subspecialties within an integrated framework, and this has been a guiding principle at the hospital as it has evolved. The success of the strategy was demonstrated in the textbook *Neurology: A Queen Square Textbook,* that Charles Clarke initiated and propelled with many others to its completion. The *Textbook* comprised 26 chapters with contributions from over 90 physicians and surgeons. This present book, *Neurology: A Clinical Handbook,* is based on the second edition of the *Textbook*. It is Charles Clarke's distillation of practical knowledge and his wide

experience. But it is more than this. This *Handbook* has the advantage of having been compiled and written by a single person, thus ensuring a seamless integration of knowledge from all the specialties. The result is a superb synopsis – a banner to herald our *Textbook* in its forthcoming Third Edition, edited by Robin Howard, Dimitri M. Kullman, David Werring and Michael Zandi.

Dr Charles Clarke is a senior neurologist who has maintained a wide-ranging general neurological practice and combined this with a knowledge of the advancing practice in the major specialist fields. Charles comes from a distinguished medical lineage and has demonstrated his skills in the production of this handbook, a consummate guide to neurological diagnosis and treatment, useful, up to date and practical, and one in which specialty knowledge has been integrated into a single framework. He has been able to bring together a text that is strikingly well balanced and authoritative. This is a crowning achievement, made possible not least because of the elegance and clarity of his writing. In the world of modern medicine, the ability to communicate clearly and precisely without savaging the beauty of the English language is a rare gift and one bestowed on Charles for all our benefit.

In all, this Handbook is a sparkling addition to the neurological library, a concise and clear guide to clinical practice in neurology, written in elegant prose, a tribute to *Queen Square* and to the contribution that both Hospital and Institute have made to neurology. It is the encapsulation of wisdom gained in a long career. For practitioners in the art of neurology, junior and senior, this is required reading.

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Queen Square, London

1

Neurology Worldwide: Public Health and Essential Neuro-epidemiology

The world over, one-third of all serious illness is caused by brain disease and a tenth by other neurological conditions. I introduce here the epidemiology and burden of neurological illness. Public Health plays a minor role in neurology. It needs more attention.

Basic Data

Incidence is new cases/100 000/year. Prevalence is the occurrence/1000 of the population, and lifetime prevalence the risk/1000 of acquiring a condition during life. These vary – between urban and rural settings and are linked to ethnicity, poverty, lifestyle/nutrition, vectors, war and sanitation. Data for specific age ranges are often more valuable than overall rates.

In the United Kingdom:

- For stroke, incidence overall is 190/100 000/year, but those over 65, 1100/100 000/year.
- For Parkinson's, incidence overall is 20/100 000/year and prevalence 2/1000. Over 65, incidence is 160/100 000/year and prevalence 10/1000.
- With epilepsy, the situation is shown in Figure 1.1.

A population's age structure impacts heavily: there are more children and young adults in poor than in rich countries (Figure 1.2). Degenerative age-related disease is increasing: the world's population over 65 is to double between 2020 and 2030. Doubling time depends upon mortality rates, on the number of offspring per mother, and on cultural, financial and religious pressure. Examples are in Table 1.1.

Practical Neurology

Practical neurology is remarkably similar the world over – a neurologist in China, India or South America will be familiar with most conditions seen in Europe (Table 1.2). Variation between regions is determined largely by infections, such as malaria. Study of the full impact of Covid-19 is unknown and not discussed here.

Neurology: A Clinical Handbook, First Edition. Charles Clarke.

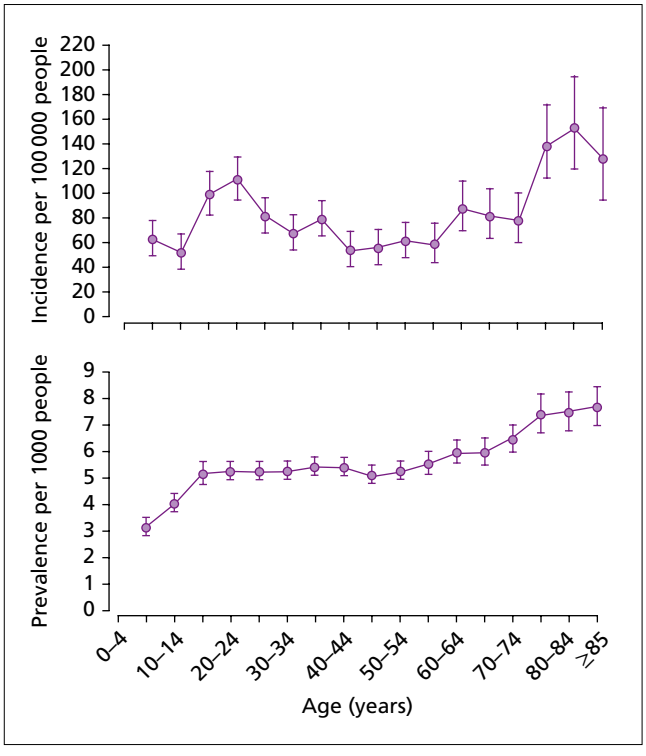

Figure 1.1 Standardized prevalence and incidence rates of treated epilepsy in a population of 2 052 922 persons in England and Wales in 1995. (Bars indicate 95% CI.) Prevalence of treated epilepsy: overall 5.15/1000 people (95% confidence interval [CI] 5.05–5.25). *Source:* Wallace *et al.* 1998.

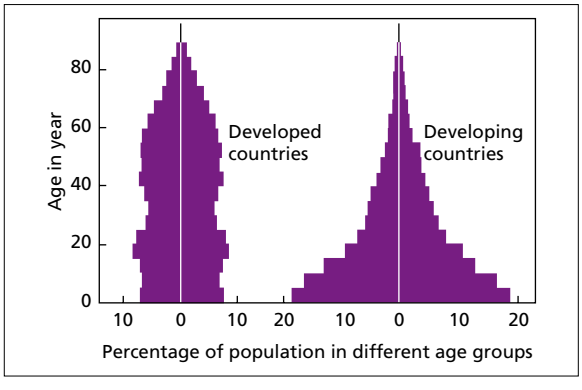

Figure 1.2 Age structure in developed (Sweden) and developing (Costa Rica) countries. *Source:* Worldwatch Database, 1996, Worldwatch Institute.

Causation

The cause of a neurological disease is rarely simple. A condition is either:

Genetic

- Huntington's: a single gene disorder with high penetrance.
- Epilepsy: complex interactions between presumed susceptibility genes.
- Alzheimer's: genetic influences in 10%, but not in the majority.

Genetic and Environmental

- Parkinson's disease: presumed genetic influences but susceptibility (curiously) reduced by smoking.

Table 1.1 Population size and doubling times.

Country	Population (millions)	No. of births/mother	Doubling time (years)
Nigeria	107	6.2	23
India	970	3.5	36
China	1236	1.8	67
USA	268	2.0	116
Japan	126	1.5	289
UK	60	1.7	433

Source: Data from The Population Reference Bureau, 2015

Table 1.2 Incidence and point prevalence.

Disorder	Incidence (100 000/year)	Point prevalence /100 000
Migraine	370	12 100
Acute stroke	190	900
Subarachnoid haemorrhage	15	
TIA	30	
Epilepsy	50	710
Dementia	50	250
Parkinson's disease	20	200
Chronic polyneuropathies	40	24
Bell's palsy	25	
Meningitis & infections	15	
Brain tumours	10	10
Trigeminal neuralgia	4	1
Multiple sclerosis	4	90
Motor neurone disease	2	4
Muscular dystrophies	1	6

Source: Data from various WHO sources; excludes shingles.

- MS: genetic susceptibility and geographic location. MS is more common in latitudes around 50°N and S of the equator, and rare in the tropics (0°–23.5° N and S). Clusters of MS cases, for example on the W coast of Ireland.

Evident and Preventable

- In traumatic brain injury, many severe brain injuries have been prevented by car seatbelts.
- Meningitis due to *Haemophilus influenza*, *Streptococcus pneumoniae* and *Meningococci*: immunisation.

Generally, where primary causes are poorly understood, causation can be divided into

- predisposing factors (e.g. age, gender, genetic susceptibility)
- enabling factors (e.g. hypertension, poor nutrition, inadequate medical care)

- precipitating factors (e.g. exposure to infectious or noxious agent)
- reinforcing factors (e.g. repeated or prolonged exposure).

Most neurological conditions are products of multifactorial influences, each of which alone would not cause the disease. It is thus helpful to study risk factors.

Mortality, Life Expectancy and Quality of Life

Mortality rate: the number dying of a condition divided by the number in the population.

This information is of limited value without knowledge of the overall death rate.

Life expectancy (median survival age) is often lowered in neurological disease, but data are complex.

Taking epilepsy, one study followed over 500 cases for >10 years. The overall mortality ratio was 2.1. The hazard ratio (HR), or risk of death, for epilepsy overall, was 6.2. Life expectancy was reduced by some 2–10 years.

Quality of Life

It is not enough to prolong survival. In high grade gliomas, radiotherapy is known to prolong life by about six months. Side effects are severe; the trade-off between survival and quality of life (QoL) is important. One study showed that how well a patient was before radiotherapy was a good indicator of disability-free life after it. For those already disabled, radiotherapy offered little gain.

Other Important Measures

- *Birth rate*: number of live births/mid-year population;
- *Fertility rate*: number of live births/number of women aged 15–44 years (Figure 1.3);
- *Infant mortality rate*: number of infant (<1 year) deaths/number of live births;
- *Stillbirth rate*: number of intrauterine deaths after 28 weeks/total births;
- *Perinatal mortality rate*: number of stillbirths + deaths in first week of life/total number of births.

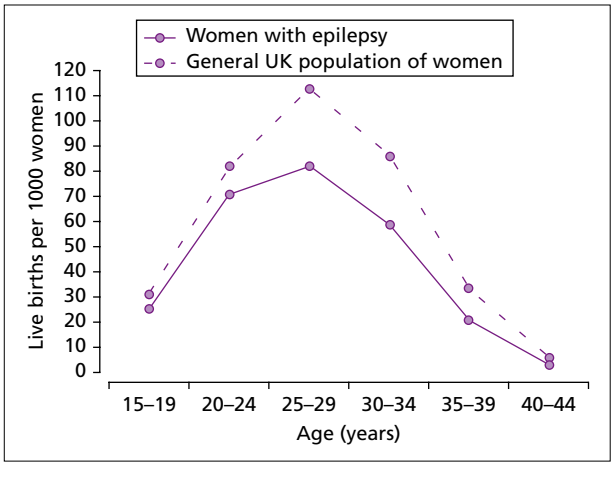

Figure 1.3 Comparison of age-specific fertility rates in women with treated epilepsy and general UK population of women in 1993.

Burden of Illness

This means all negative impacts, though the words are often used to define cost. Whilst cost studies produce fiscal measurements, it is absurd to measure QoL in cash. Utility measures such as quality-adjusted life years (QALYs) and disability-adjusted life years [DALYs] try to quantify this burden (Table 1.3).

Cost of Illness Studies

The principal duty of a clinician is to provide individual care. However, doctors are now rightly involved in economic considerations. In any study of cost, analysis is of signal importance. Who was the study for, and who did it? The cost and burden for an individual have different parameters when compared with the effect on families, on health services and on society. Many studies are carried out from the point of view of society, with costs estimated in terms of lost employment, lost productivity and premature death, rather from the perspective of a patient, or their family.

- Direct costs mean any resource used – medical costs of primary care, out-patient and in-patient investigation, drugs, residential and community care, training and rehabilitation.
- Indirect costs are from lost economic production. They include premature mortality, dependency, unemployment and underemployment. The 'human capital' approach ascribes a monetary value to a person in terms of their potential productivity.

Table 1.3 DALYs (Disability-Adjusted Life Year) for neurological and psychiatric conditions.

	DALYs × 10				
Condition	**Europe**	**Wealthy countries[a]**	**India**	**Sub-Saharan Africa**	**World**
Neurological and psychiatric conditions (all)[b]	53 009	24 682	23 949	15 788	165 082
Cerebrovascular disease	10 316	5166	5223	5487	45 770
Unipolar depression	4091	6721	10 064	6193	60 166
Bipolar disease	1541	1673	2867	1,785	16 722
Schizophrenia	1609	2151	2041	611	14 614
Epilepsy	633	427	848	526	4712
Alcoholism	4435	4611	1113	2387	18,973
Dementia	4531	3286	1192	453	10 135
Parkinson's disease	428	523	167	63	1278
Multiple sclerosis	303	222	253	140	1569

[a] Established market economies.
[b] This category excludes cerebrovascular disease.
Disability-adjusted life year is an indicator of the time lived with a disability and the time lost due to premature mortality. Reproduced with permission from the World Health Organization 1996b. The figures for Europe were separately calculated (Olesen and Leonardi 2003). *Source:* Modified from Olesen and Leonardi 2003.

Ethical and personal issues are intertwined with cost-effectiveness. Therapies that are neither cost-effective from the epidemiological nor from point of view of society can help an individual – such as the belief in homeopathic therapy, or travel to a centre for healing. Societal and evidence-based, clinical perspectives clash.

Social policy can greatly lessen the individual burden, for example by financial benefits and social support. It must be stressed that in the majority of countries, even those who pride themselves on wealth and power, there is either no or minimal support for those who are ill, either acutely or chronically.

Stigma

Disease burden includes psychological, social, employment and legislative aspects. Some are rational, for example driving restrictions in epilepsy or stroke.

Stigma and discrimination deserve mention:

- enacted stigma – discrimination experience for example 'does he (the man in the wheelchair) take sugar?'
- felt stigma – discrimination fear
- self-stigma – shame/withdrawal – response to discrimination perceived.

Complex interactions construct a stigma theory – to explain potential dangers people represent, either to others or to themselves. Whilst many no longer believe in witchcraft, in life after death, in the power of prayer or of the devil, some still do, and there remains a view that someone with a condition such as epilepsy, mental sub-normality or schizophrenia is in some way to blame.

Epilepsy is one example. To be regarded as *epileptic* can be more devastating than having *an occasional blackout*. Such beliefs are not restricted to poor societies. In Europe, with epilepsy, over 50% feel stigmatised. In the United States in some states until the 1950s, people with epilepsy were prohibited from marrying and could be sterilised; until the 1970s they could be excluded from restaurants and theatres.

Headache is another: people with headaches feel stigmatised at work. There is the well-known male attitude to women with headaches and menstrual discomfort.

Doctors and health professional should be aware, not only of such prejudices, but also of their own attitudes.

Costs and Impact

Ill health imposes high costs, both on the patient and family everywhere. However, in poorer countries the proportion of family income spent on health is particularly high, not least as ill health results in unemployment.

- In the United Kingdom, any chronic illness (over one year) is likely to diminish the income of a family by >50%.

Even in countries where health services are free at the point of delivery, the cost of all illness is substantial.

Neurological illnesses because of their chronic nature are particularly onerous. The impact of a disease depends upon personal wealth, the healthcare system and social networks available.

Treatment Gaps

Taking epilepsy again, a Treatment Gap is the percentage with seizures who do not receive anti-epileptic drugs (AEDs). In Pakistan, the Philippines and Ecuador there are epilepsy TGs of 80–95%, in India around 75%, but <5% in the United Kingdom, pre-COVID. Reasons include lack of health care, cost, drug availability, cultural factors, and stigma – and failure to grasp that AEDS are effective. Campaigns to narrow TGs are priorities.

Improvements

Improvements in health delivery rest largely with governments, their knowledge and resources. Non-provision is largely due to policies. Success or failure to deliver provides stark contrasts, often unrelated to GDP. Most European countries have integrated care systems, that aim to improve the health of the populace. So does Cuba, despite its poverty. In the US, despite some of the world's finest medical institutions such a system remains in its infancy. Quite where we are heading in the United Kingdom and in Europe, from 2021, is known to no one.

Acknowledgements

I am indebted to Professor Simon Shorvon who wrote the original chapter in *Neurology A Queen Square Textbook* Second Edition. Edited by Charles Clarke, Robin Howard, Martin Rossor & Simon Shorvon, Wiley Blackwell, 2016.

I am also most grateful to Dame Sally Davies, former Chief Medical of Health for England and to Dr Elizabeth Davies, Reader in Cancer & Public Health, King's College, London who reviewed and commented on my text.

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2

Movement, Sensation and The Silent Brain

Anatomical complexities of the nervous system became apparent in the late nineteenth century. Highlights were the pathways described by Santiago Ramón y Cajal in the 1890s and later the cortical mapping by Brodmann and the work of Alf Brodal. However, remarkably little neuroanatomy was required to practice sensibly and safely. To an extent this remains so. The neuroanatomy here is in excess of the needs of most general neurologists but further study is essential in many aspects of neuroscience.

First, here is an overview of the motor and sensory pathways of the brain and cord – the basic wiring that must be understood. I deal with this largely as illustrations. I also summarise what I call the Silent Brain, vital but less obvious – regions such as the thalamus. Cortical function is dealt with in Chapter 5. For neurones, nerves, glia and myelin see Chapter 10. Chapter 13 deals with the cranial nerves. Neuro-ophthalmology is in Chapter 14, Neuro-Otology in Chapter 15 and the autonomic nervous system in Chapter 24.

The overall anatomy of the brain is illustrated in Figure 2.1.

ABC of Movement: Cortical, Extrapyramidal and Cerebellar Function

Movement – skilled, coordinated and fast – is highly developed in mammals. Rudimentary objectives are feeding, survival and reproduction and in Mankind, skilled use of tools, weapons and instruments of creative art.

A) Corticospinal (pyramidal) tracts originate in the motor cortex, somatosensory and limbic areas to reach cranial nerve nuclei and cord anterior horn cells. Dysfunction produces loss of skilled movement, weakness, spasticity and reflex change.
   Pyramidal describes the triangular cross-section of the tract in the medulla. Pyramidal is used here interchangeably with corticospinal.
B) The striatal (a.k.a. extrapyramidal) system facilitates fast, fluid movement. Hallmarks of dysfunction are slowness (bradykinesia), stiffness (rigidity), rest tremor, all seen typically in Parkinson's and some movement disorders. Broadly, these are basal ganglia functions.
C) The cerebellum coordinates smooth movement, and balance. Ataxia and action tremor are features of dysfunction.

Neurology: A Clinical Handbook, First Edition. Charles Clarke.

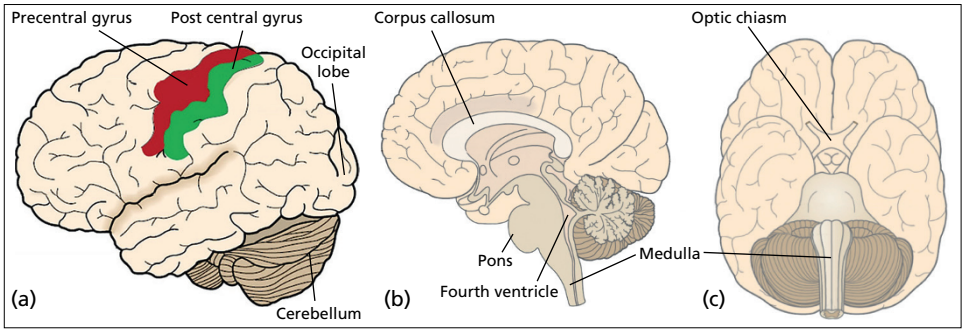

Figure 2.1 Brain: overall anatomy (a) Lateral view (b) Midsagittal section (c) Ventral view. *Source*: Champney (2016).

Cortex: Movement Force, Direction and Synergy

Movements are produced by neuronal groups in the motor cortex. These groups act synergistically to control force, direction and timing – and they communicate with sensation – to produce fine, skilled movements.

Pyramidal System Anatomy

Figure 2.2 outlines the principal motor pathway from cortex to anterior horn cells.

Note:

- Pyramid: within rostral medulla
- Decussation of the pyramids: within caudal medulla
- Cortico-spinal axons synapse on cord anterior horn cells.

Extrapyramidal System and Basal Ganglia Region

The word extrapyramidal is used in various ways. In neurology, extrapyramidal describes disorders such as Parkinson's disease – the slowing, stiffness and/or tremor. Extrapyramidal is also sometimes used to include dyskinesias, such as chorea, hemiballismus or dystonia. In neuroanatomy, as a more general term, extrapyramidal relates to the basal ganglia region (Figure 2.3), that is:

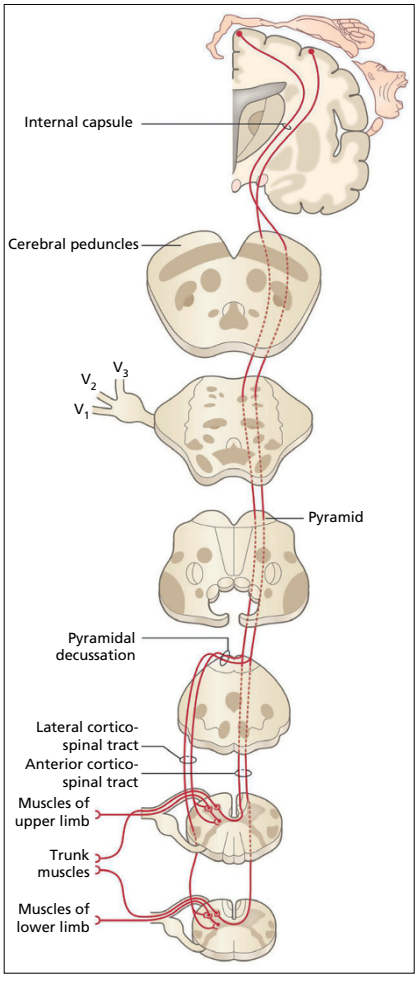

Figure 2.2 Descending corticospinal pathways. *Source*: Champney (2016).

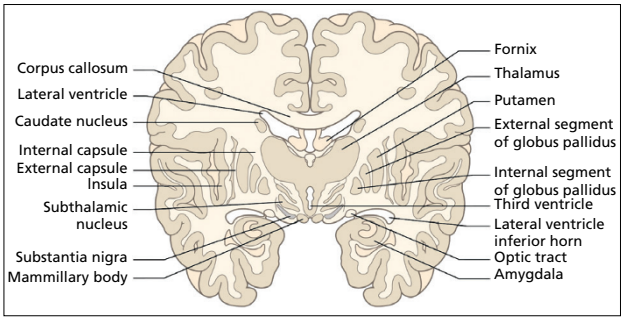

Figure 2.3 Oblique coronal section: *putamen*, caudate, *globus pallidus,* subthalamic nucleus, *substantia nigra*. *Source*: Champney (2016).

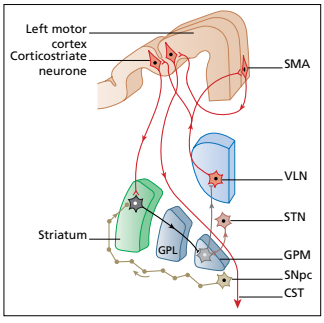

Figure 2.4 A striatal motor loop. SMA - supplementary motor area, VLN - ventral lateral nucleus of thalamus, STN - subthalamic nucleus, GPL - *globus pallidus* (lateral), GPM - *globus pallidus* (medial), SNpc - *substantia nigra pars compacta*, CST- corticospinal tract. *Source*: Fitzgerald (2010).

- The *striatum* (caudate nucleus, *putamen* of lentiform nucleus, *nucleus accumbens*);
- *Globus pallidus* (GP) – lateral and medial parts. The GP extends into the *pars reticularis* of the *substantia nigra*;
- Subthalamic nucleus
- *Pars compacta* of the *substantia nigra.*

Basal Ganglia Circuits

Neuronal servo-loops commence and end in the motor cortex. All pass through the striatum (*putamen* + caudate nucleus) and return via the thalamus, and within each loop there are two pathways: direct and indirect.

Transmission through each loop is controlled via the *pars compacta* of the *substantia nigra* to the lateral *globus pallidus*, where axons make two principal types of synapse, on excitatory D_1 (dopaminergic, direct pathway) and inhibitory D_2 (indirect pathway) receptors. Further receptors are now recognised in the D receptor series.

In normal subjects, the nigro-striatal tract is active, selecting preferentially the excitatory, direct pathway and thus leading, via the loop back to the cortex to activation of the supplementary motor area before a movement, and thence to a movement itself (Figure 2.4). This early activation of the cortex underlies the electrical readiness potential (*Bereitschaftspotential*).

Such servo-loops modulate, for example:

- Cognition/motor intention, contraction strength, suppression, speed control, storage of programmes
- Limbic (memory) loop: cortex→*nucleus accumbens*→ventral *pallidum*→thalamus→cortex.

Cerebellar System

Zones of the cerebellum are illustrated in Figure 2.5.
The cerebellar peduncles and deep cerebellar nuclei are shown in Figure 2.6.
The essential cellular anatomy of the cerebellar cortex is shown in Figure 2.7.

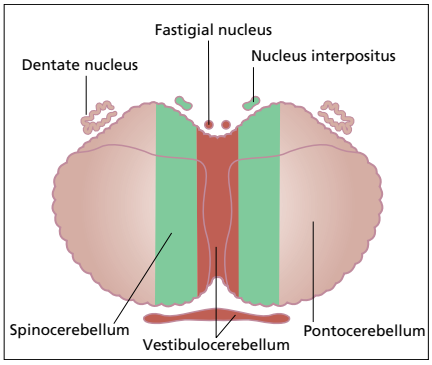

Figure 2.5 Zones of the cerebellum. *Source*: Fitzgerald (2010).

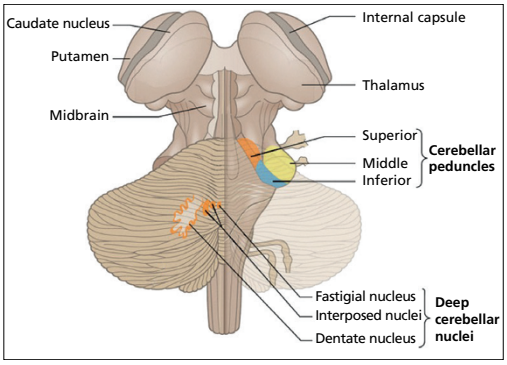

Figure 2.6 Cerebellar peduncles & nuclei: posterior view. *Source*: Champney (2016).

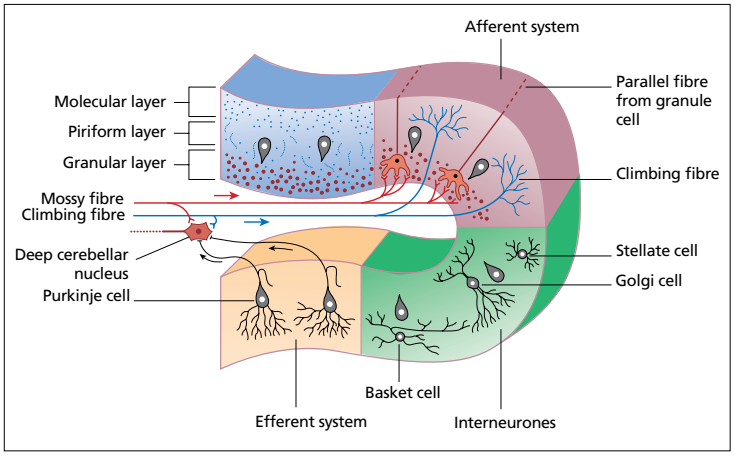

Figure 2.7 Cerebellum: cortical micro-anatomy. *Source*: Fitzgerald (2010).

Afferent and Efferent Cerebellar Pathways

Afferent pathways include:

- Spino-cerebellar: posterior and anterior spino-cerebellar tracts – proprioceptive data from spinal cord.
- Ponto-cerebellar: originates in the cerebral cortex, and enters via middle cerebellar peduncle.
- Vestibulo-cerebellar: vestibular nuclei, enters via inferior peduncle.

Efferent pathways project to the vestibular system, to the cord, thalamus, motor cortex and to the red nucleus,.

The cerebellum and red nucleus in the midbrain tegmentum have a role in learned movement. The system modulates new motor activity:

- The red nucleus is a relay between cerebral cortex and the olive – the red nucleus is inhibitory, to the ipsilateral olive.
- When there is imbalance between movement intended (cerebral cortex) and movement already learned (cerebellum), the red nucleus is thought to modulate, to achieve harmony.
- A lesion of the red nucleus – a coarse tremor – is a breakdown of this harmonic, overcorrecting each part of a movement.

In contrast to the anatomical complexity, signs of cerebellar disease are usually straightforward:

- A lateral lobe lesion – a tumour or an infarct – causes rebound and past pointing of the upper limb and similar lower limb signs.
- A vermis lesion – for example midline medulloblastoma – affects vestibular connection: truncal ataxia can be an early sign.
- Nystagmus – coarse, fast phase towards the side of a lesion, sometimes dramatic – is an inconstant feature.

Sensory Pathways

Neurologists deal with the special senses – vision, hearing/balance, olfaction and taste – and the main five sensory modalities: touch, nociception, temperature, joint position, vibration and two-point position. Neuroscientists use an alternative vocabulary: sensation is either conscious or non-conscious and either afferent proprioceptive – from a limb, or enteroceptive – from gut, or heart.

Sensory Pathways in the Cord and Brain

Two major pathways deliver sensory information to the thalamus and thence to the cortex (Figure 2.8):

- Spinothalamic pathways (nociceptive – pain, temperature);
- Posterior columns → medial lemnisci (touch, position, movement, vibration).

Each system consists of three orders of neurones.

- First order neurones are in the posterior root (dorsal root) ganglia;
- Second order neurones decussate before reaching the thalamus;
- Third order neurones project from thalamus to cortex;

There is somatotopic organisation throughout, and transmission can be controlled (inhibited/enhanced) at various stages (see Gate Control & Chapter 23).

Dorsal Root Ganglia

The complexity of the laminae within the posterior horn and the cord pathways are illustrated in Figure 2.9, the detail of which is hard to remember. A single nerve root ganglion can contain around 100,000 neurones, each enshrouded by a modified Schwann cell. Two

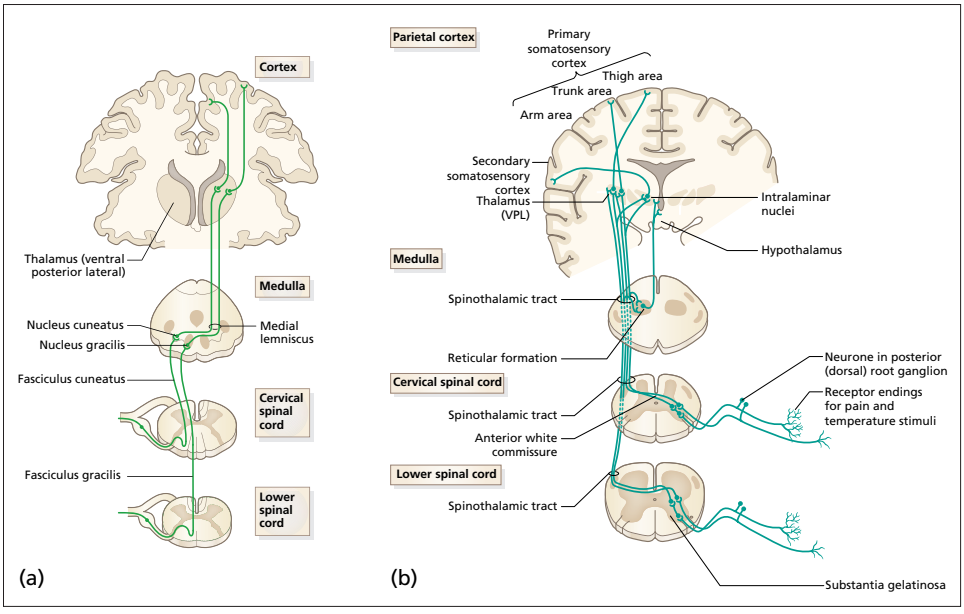

Figure 2.8 Sensory pathways to the cortex. (a) Posterior columns, (b) Spinothalamic tracts. *Source*: Champney (2016).

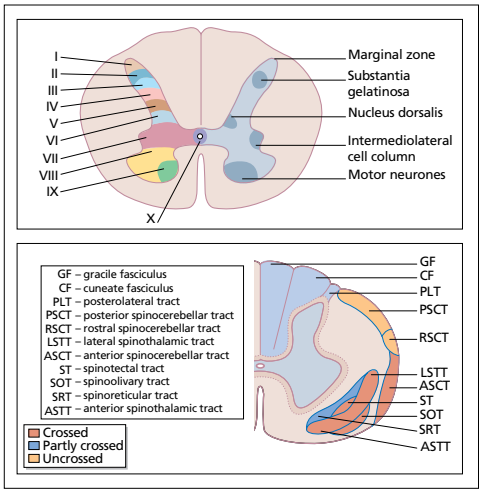

Figure 2.9 Cord cross-section: dorsal horn laminae, ascending & descending tracts. *Source*: Fitzgerald 2010.

streams of axons, medial and lateral – the dorsal root afferents – synapse in various specific areas of the cord, to form the two main sensory pathways.

Posterior Column→Medial Lemniscus Pathway

The cord posterior columns are formed partly by axons of posterior root ganglia and partly by axons of second order neurones in the dorsal horn of the spinal grey matter. These axons all project to the gracile and cuneate nuclei in the brainstem. Axons then decussate in the medulla to form each medial lemniscus (meniscus means a ribbon) that terminates in the ventral posterior nucleus of the thalamus. Thalamic neurones then project to the somatic sensory cortex.

Spinothalamic Pathway

The anterior and lateral spinothalamic tracts pass from the posterior grey horn to the opposite thalamus. The two tracts merge in the brainstem to form the spinal lemniscus, enter the ventral posterior nucleus of the thalamus and project to the somatic sensory cortex.

Additional sensory pathways are concerned with non-conscious proprioception, reflex arc excitability, balance between agonists and antagonists, trunk and head orientation, arousal & motor learning:

- Posterior spino-cerebellar tract, cuneo-cerebellar tract, anterior spino-cerebellar tract, rostral spino-cerebellar tract
- Spino-tectal tract, spino-olivary tract, spino-reticular fibres.

We cannot recognise lesions of these pathways clinically – they are part of the wider framework of motor and sensory modulation.

The Silent Brain

This section summarises the functional anatomy of the brainstem, reticular formation, limbic system and hippocampus, thalamus, hypothalamus, pituitary, and the little known circumventricular organs – regions I call The Silent Brain.

Brainstem

I find that four points of reference simplify this region:

- Each cranial nerve nucleus denotes a different level in the rostral–caudal plane.
- Motor pathways lie ventrally.
- Sensory pathways lie dorsally.
- Reticular formation (RF) nuclei: most lie laterally, but the magnus raphe & median raphe nuclei are midline.

In our invertebrate ancestors, the brainstem was almost the entire forebrain. Olfaction and other sensations were connected, via the brainstem reticular formation (RF) to various movements – and thus to alertness, feeding and survival. With the evolution of the cerebral cortex, the brainstem became, in addition, a conduit connecting cranial nerve nuclei, cortex, cerebellum and cord, but remained the site of the RF and its connections – hence its complexity. What is needed is a general grasp of the levels of these brainstem nuclei (Figure 2.10).

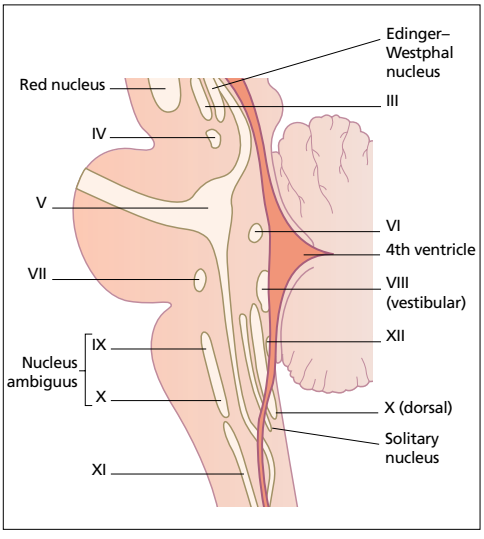

Figure 2.10 Brainstem: lateral view – cranial nerve nuclei. *Source*: Hopkins (1993).

The way in which the nuclear arrangements arose is explained by a brief embryological perspective. Seven nuclear columns develop into cranial nerve nuclei.

Motor cranial nerve nuclei:

- III, IV, VI and XII arise from a paramedian nuclear mass – known as the general somatic efferent (GSE) column.
- V (motor), VII, IX and X (nucleus ambiguus) and XI (spinal accessory nucleus) arise from ventro-lateral cells – the special visceral efferent (SVE) and general visceral efferent (GVE) columns.

Afferent columns (general & special somatic and visceral afferents – GSA, SSA, SVA, GVA) develop into:

- Vth nerve nuclei
- Vestibular nuclei
- Tractus solitarius nucleus (taste).

Reticular Formation

The RF has no single overriding function – and no single condition becomes apparent when it is damaged. It is a control centre, a polysynaptic network within the thalamus, hypothalamus, brainstem and cord involved in:

- Respiratory and cardiovascular control
- Sleep, wakefulness, arousal and mood
- Pattern generation – reflex activities, for example chewing, swallowing, conjugate gaze
- Micturition, bowel and sexual function
- Sensory modulation (see Gate control below, and Chapter 23)
- Autonomic and reflex activity (Chapter 24).

Essential anatomy and neurotransmitters: Figure 2.11 The raphe nuclei (pronounced 'raffay' = a seam in Greek) are the major source of serotoninergic neurones in the neuraxis.

Gate Control: Sensory Modulation

Gating (also Chapter 23) means control of synaptic transmission between one set of neurones and the next. The RF has a role in gating sensory stimuli.

- Tactile sensation is gated at the posterior column nuclei. Nociceptive transmission from the trunk and limbs is gated in the posterior grey horn of the cord, and from the head in the spinal V nucleus. One crucial cord structure is the *substantia gelatinosa,* rich in excitatory glutaminergic neurones and inhibitory GABAergic and enkephalinergic neurones.
- Unmyelinated C fibres mediate dull, intense, prolonged, poorly localised pain. Short, sharp, well-localized pain is mediated by finely myelinated Aδ fibres. These synapse directly on relay neurones of the lateral spinothalamic tract.
- Large A (mechano-receptor) afferents from hair follicles and skin synapse on anterior spinothalamic cells and send collaterals to inhibitory (GABAergic) gelatinosa cells. These then synapse on lateral spinothalamic tract relay cells.
- Enhancement of RF inhibition from the magnus raphe nucleus, by rubbing, TENS, implanted stimulators, sleep and pain-modulating drugs reduces – that is, gates – C fibre activity.